Estimating time of HIV-1 infection in infants using viral sequence diversity

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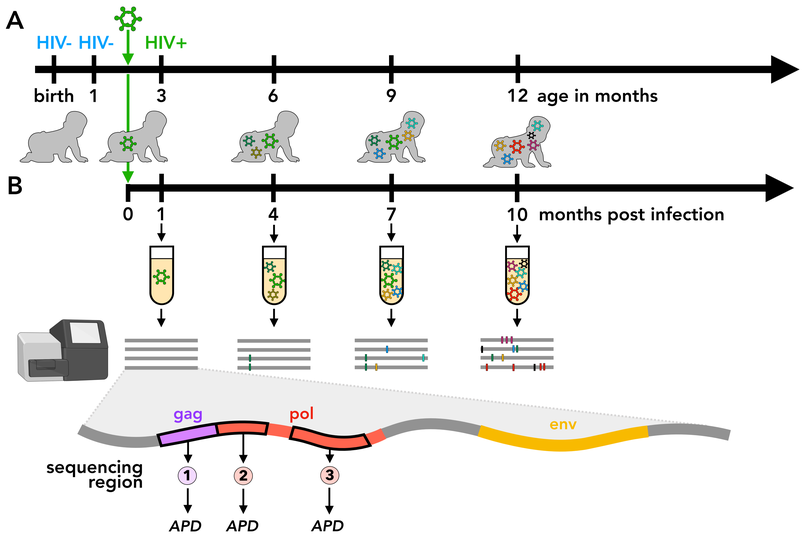
BACKGROUND

Infants born to mothers living with HIV are at risk for acquiring HIV in utero or during delivery and breastfeeding, however, the precise time of infant infection is often unknown. Adult studies have accurately estimated infection timing using rates of viral diversification, however, rates of viral diversification in infants are not well defined and likely differ from adults. As such, existing adult models have low prediction accuracy when used for infants. Because infant HIV is associated with higher viral load than adults, **we hypothesized that an infant-specific model using viral sequence diversity would more accurately predict infection time for infants than adult-specific models.**



PARTICIPANT SAMPLES

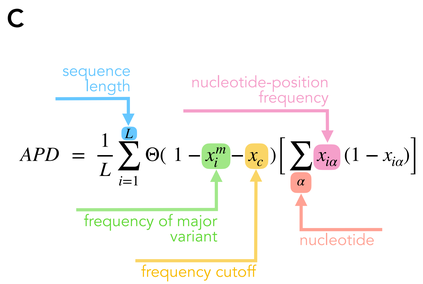
A Kenyan cohort of children born to mothers living with HIV were followed from birth through age two with frequent HIV testing and banked plasma sample (**A**). Because antiretroviral therapy (ART) was not yet standard of care in Kenya during the time frame (1999-2002), the children were ART-naive for the duration of monitoring. Frequent HIV testing allowed us to estimate the time of HIV infection as the midpoint between the last negative HIV test (DNA or RNA) and the first positive test.

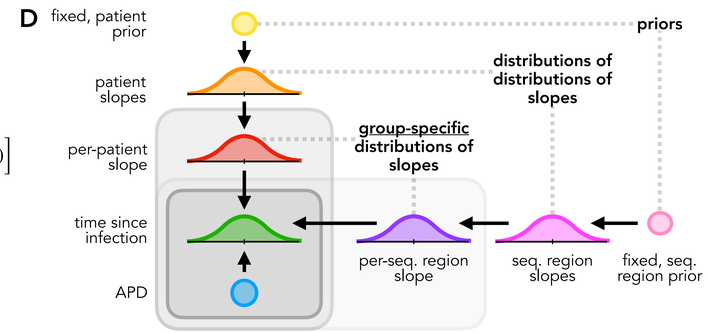
SEQUENCING METHODS

Using Illumina sequencing of three regions within *gag* and *pol* (roughly 4 kb total) from longitudinal plasma samples collected between 1-24 months of age from 18 Kenyan infants with defined infection timing (11 infected in utero, 3 infected between 3-6 months, and 4 infected between 6-12 months), we estimated the average pairwise diversity (APD) of the viral population within each sample time-point (**B, C**).

MODELING METHODS

We designed an infant-specific Bayesian hierarchical regression model (**D**) that predicts time since infection using viral APD (**C**). We validated this model using leave-one-out cross validation (LOOCV), and compared the infection time estimates from our model to estimates for each infant inferred using an adult-specific model (Puller et al, 2017).

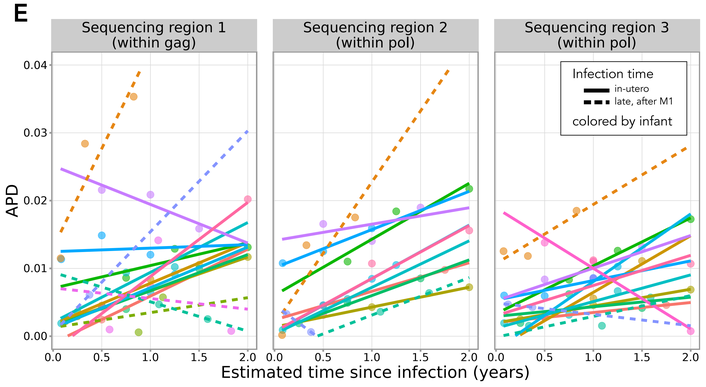


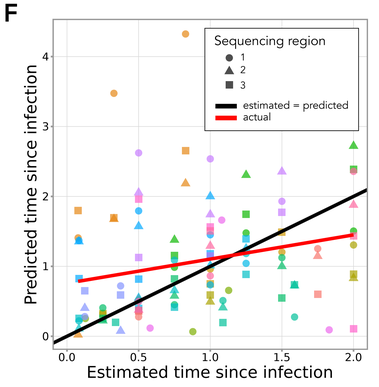


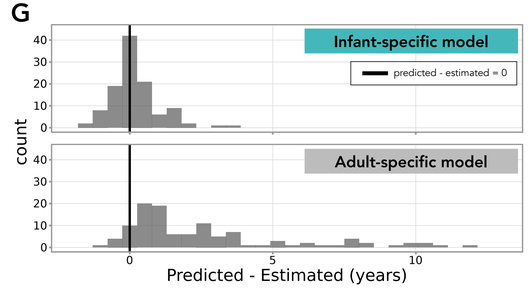
Our **infant-specific model** uses viral sequence diversity to **predict time since HIV infection for infants more accurately** than existing **adult-specific models.**

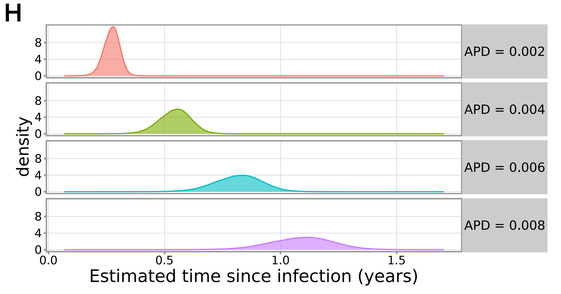
RESULTS

Viral diversity over time, as measured by APD, increased at a mean rate of 0.003 diversity/year (CI = [0.001 - 0.005], p = 0.004) across all infants and sequence regions during the first 2 years of infection. This rate was significantly higher for infants infected in utero than infants infected after birth (0.003 vs. 0.001 diversity/year, p = 0.006). Rates also varied significantly between infants (range = -0.003-0.026, p = 1.5e-12) and sequence regions (range = 0.002-0.004, p = 0.006) (**E**). We incorporated this variation into our model framework. Our infant-specific model predicts time since infection for infants more accurately (mean absolute error = 7 months using LOOCV) than existing adult-specific models (mean absolute error = 32.4 months) (**F, G**). With our Bayesian modeling approach, we can also assess the probability of all possible infection times for any given APD (**H**).









CONCLUSIONS

Here, we have shown that viral APD can be used to estimate time since infection for infants more accurately using our infant-specific model compared to adult-specific models. Our model will be useful for predicting time of HIV infection for infants with unknown timing.

ADDITIONAL KEY INFORMATION

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